

**Systems and Methods for Treatment of Obesity and Eating Disorders
by Electrical Brain Stimulation and/or Drug Infusion**

[0001] The present application claims the benefit of U.S. Provisional Patent Application Serial Number 60/252,625, filed November 21, 2000, which application is incorporated herein by reference in its entirety.

Field of the Invention

[0002] The present invention generally relates to drug delivery and electrical stimulation systems and methods, and more particularly relates to utilizing one or more devices to deliver electrical stimulation and/or one or more stimulating drugs to certain areas of the brain as a treatment for obesity and/or other eating disorders.

Background of the Invention

[0003] Obesity affects millions of Americans, and a substantial percentage of these people are morbidly obese, suffering such obesity-related problems as heart disease, vascular disease, and social isolation. An additional number of Americans suffer from various other eating disorders that may result in cachexia (i.e., a general physical wasting and malnutrition) or periods of obesity and/or cachexia. The etiology of obesity is largely unknown. The etiology of some eating disorders is psychological in many patients, but for other patients, is poorly understood.

[0004] Patients suffering from morbid obesity and/or other eating disorders have very limited treatment options. For instance, some of these patients may undergo surgery to reduce the effective size of the stomach ("stomach stapling") and to reduce the length of the nutrient-absorbing small intestine. Such highly invasive surgery is associated with both acute and chronic complications, including infection, digestive problems, and deficiency in essential nutrients. In extreme cases, patients may require surgical intervention to put a feeding tube in place. Patients suffering from eating disorders may suffer long-term complications such as osteoporosis. Additional treatment options are needed.

Summary of the Invention

[0005] The invention disclosed and claimed herein provides systems and methods for introducing one or more stimulating drugs and/or applying electrical stimulation to one or more areas of the brain for treating or preventing obesity and/or other eating disorders, as well as the symptoms and pathological consequences thereof. Proper stimulation of specific sites in the brain via Deep Brain Stimulation (DBS) may lead to changes in levels or responses to neurotransmitters, hormones, and/or other substances in the body that treat eating disorders.

[0006] The invention is carried out via one or more system control units (SCUs) that apply electrical stimulation and/or one or more stimulating drugs to one or more predetermined stimulation sites in the brain, for instance, to an appropriate area of the hypothalamus. In some forms of an SCU, one or more electrodes are surgically implanted to provide electrical stimulation from an implantable signal/pulse generator (IPG) and/or one or more infusion outlets and/or catheters are surgically implanted to infuse drug(s) from an implantable pump. In other forms of an SCU, a miniature implantable neurostimulator (a.k.a., a microstimulator), such as a Bionic Neuron (also referred to as a BION[®] microstimulator), is implanted. Some forms of the disclosed systems also include one or more sensors for sensing symptoms or conditions that may indicate a needed treatment.

[0007] An SCU may provide both electrical stimulation and one or more stimulating drugs when necessary and/or desired. In some embodiments, the SCU is implanted in a surgically-created shallow depression or opening in the skull, such as in the temporal, parietal, or frontal bone. In some such embodiments, one or more electrode leads and/or catheters attached to the SCU run subcutaneously to an opening in the skull and pass through the opening into or onto the brain parenchyma and surrounding tissue.

[0008] Patients with an eating disorder(s) will likely respond to therapeutic excitatory stimulation applied to those areas of the brain that exhibit chronic decreased activity relative to normal control subjects. Thus, according to certain embodiments of the invention, the stimulation increases excitement of one or more of those areas of the brain that exhibit chronic decreased activity in patients relative to normal control

subjects, thereby treating or preventing eating disorders and/or the symptoms and/or consequences thereof. Such excitatory stimulation is likely to be produced by, for example, low-frequency electrical stimulation, an excitatory neurotransmitter agonist, and/or an excitatory hormone agonist. Additional potential (but not necessary) uses of the present invention include, but are not limited to, treatment for and prevention of diabetes and other conditions caused or worsened by eating disorders, via the promotion of normal metabolism and weight control.

[0009] Patients with an eating disorder(s) will likely respond to therapeutic inhibitory stimulation applied to those areas of the brain that exhibit chronic *increased* activity relative to normal control subjects. Thus, according to various embodiments of the invention, the stimulation decreases excitement of one or more of those areas of the brain that exhibit chronic increased activity in patients relative to normal control subjects, thereby treating or preventing eating disorders and/or the symptoms and/or consequences thereof. Such inhibitory stimulation is likely to be produced by, for example, high-frequency electrical stimulation, an inhibitory neurotransmitter agonist, and/or an inhibitory hormone agonist. Again, additional potential (but not necessary) uses include, but are not limited to, treatment for and prevention of conditions caused or worsened by eating disorders, via the promotion of normal metabolism and weight control.

[0010] The SCU may include a programmable memory for storing data and/or control parameters. This allows stimulation and control parameters to be adjusted to levels that are safe and efficacious with minimal discomfort. Electrical and drug stimulation may be controlled independently; alternatively, electrical and drug stimulation may be coupled, e.g., electrical stimulation may be programmed to occur only during drug infusion.

[0011] According to some embodiments of the invention, the electrodes used for electrical stimulation are arranged as an array on a thin implantable lead. The SCU may be programmed to produce either monopolar electrical stimulation, e.g., using the SCU case as an indifferent electrode, or bipolar electrical stimulation, e.g., using one of the electrodes of the electrode array as an indifferent electrode. The SCU may include a means of stimulating a nerve or infusing a stimulating drug(s) either intermittently or

continuously. Specific stimulation/infusion parameters may provide therapy for, e.g., varying types and degrees of severity of eating disorders.

[0012] The SCU used with the present invention possesses one or more of the following properties, among other properties:

[0013] at least two electrodes for applying stimulating current to surrounding tissue and/or a pump and at least one outlet for delivering a drug or drugs to surrounding tissue;

[0014] electronic and/or mechanical components encapsulated in a hermetic package made from biocompatible material(s);

[0015] an electrical coil inside the package that receives power and/or data by inductive or radio-frequency (RF) coupling to a transmitting coil placed outside the body, avoiding the need for electrical leads to connect devices to a central implanted or external controller;

[0016] means for receiving and/or transmitting signals via telemetry;

[0017] means for receiving and/or storing electrical power within the SCU; and

[0018] a form factor making the SCU implantable in a depression or opening in the skull, or within the brain.

[0019] The power source of the SCU is realized using one or more of the following options, or the like:

[0020] (1) an external power source coupled to the SCU via a radio-frequency (RF) link;

[0021] (2) a self-contained power source made using any means of generation or storage of energy, e.g., a primary battery, a replenishable or rechargeable battery, a capacitor, a supercapacitor; and/or

[0022] (3) if the self-contained power source is replenishable or rechargeable, a means of replenishing or recharging the power source, e.g., an RF link, an optical link, or other energy-coupling link.

[0023] According to certain embodiments of the invention, an SCU operates independently. According to various embodiments of the invention, an SCU operates in a coordinated manner with other implanted SCUs, other implanted devices, or with devices external to the patient's body.

[0024] According to several embodiments of the invention, an SCU incorporates means of sensing the disorder or symptoms thereof, or other measures of the state of the patient. Sensed information may be used to control the electrical and/or drug stimulation parameters of the SCU in a closed loop manner. According to some embodiments of the invention, the sensing and stimulating means are incorporated into a single SCU. According to several embodiments of the invention, the sensing means communicates sensed information to at least one SCU with stimulating means.

Brief Description of the Drawings

[0025] The above and other aspects of the present invention will be more apparent from the following more particular description thereof, presented in conjunction with the following drawings wherein:

[0026] FIG. 1A depicts the dorsal surface of the brain stem;

[0027] FIG. 1B is a section view through the brain stem depicted in FIG. 1A;

[0028] FIG. 2A depicts the medial surface of the brain stem;

[0029] FIG. 2B is a section view through the brain stem depicted in FIG. 2A;

[0030] FIGS. 3A, 3B, and 3C show some possible configurations of an implantable microstimulator of the present invention;

[0031] FIG. 4 illustrates a lateral view of the skull and components of some embodiments of the invention;

[0032] FIG. 5 illustrates internal and external components of certain embodiments of the invention;

[0033] FIG. 6 illustrates external components of various embodiments of the invention; and

[0034] FIG. 7 depicts a system of implantable devices that communicate with each other and/or with external control/programming devices.

[0035] Corresponding reference characters indicate corresponding components throughout the several views of the drawings.

Detailed Description of the Invention

[0036] The following description is of the best mode presently contemplated for carrying out the invention. This description is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles of the invention. The scope of the invention should be determined with reference to the claims.

[0037] The hypothalamus has been demonstrated experimentally in animal studies to exert significant control over feeding behavior. In addition, it is hypothesized that the hypothalamus controls a variety of bodily and cellular functions (e.g., metabolic rate) in order to maintain a set-point for body weight. The hypothalamus is divided into small functional collections of cells known as nuclei; in patients with eating disorders, one or more nuclei in the hypothalamus may demonstrate abnormal behavior.

[0038] Some of the neurons in the arcuate nucleus of the hypothalamus secrete a neurotransmitter known as Neuropeptide Y (NPY). These NPY-secreting neurons project to several other hypothalamic nuclei. Increased secretion of NPY leads to abnormally increased appetite for food (hyperphagia), increased body weight, and reduced energy expenditure. In fact, NPY is the most potent central (i.e., acts in the brain/spinal cord) appetite stimulant known. In addition, it is believed that unfavorable metabolic situations, such as diabetes, produce enhanced NPY gene expression and NPY release in the hypothalamus.

[0039] NPY also leads to endocrinological disturbances, including increased secretion of adrenocorticotrophic hormone (ACTH) and glucocorticoids, and decreased secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), and thyroid stimulating hormone (TSH). Increased levels of glucocorticoids stimulate feeding, favor fat accumulation, and are essential to the development of obesity syndromes in rats. ACTH and glucocorticoid levels have been found to be increased in patients with eating disorders.

[0040] Leptin, a protein secreted by adipose (i.e., fat) cells, is believed to inhibit NPY neurons in the arcuate nucleus. In normal subjects, leptin acts via the leptin

arcuate nucleus and the paraventricular nucleus receive serotonergic input from fibers in the raphe nuclei in the brainstem. The ventromedial nucleus and the paraventricular nucleus also receive a cholecystokinin-containing projection relayed from the vagal nuclei via the parabrachial nucleus in the pons (i.e., the pontine taste center).

[0047] Ghrelin, a peptide hormone, has been shown to increase food intake in rats under conditions of both fasting and satiety. Furthermore, ghrelin antagonists have been demonstrated to suppress feeding in rats. Ghrelin acts on the arcuate nucleus in the hypothalamus, among other sites, and appears to act as a leptin antagonist.

[0048] Agouti-Related Protein (AGRP) is present in increased levels in obese and diabetic mice. It is produced in the hypothalamic arcuate nucleus and can stimulate hyperphagia when over expressed. The type of AGRP produced may vary slightly between individual humans; the variation may be as minor as a difference in one amino acid in the protein. One of these types has been demonstrated to be significantly associated with high body mass index (BMI, a measure of obesity) and type 2 diabetes in Africans. AGRP switches off the melanocortin 4 receptor (MC4-R) and possibly the melanocortin 3 receptor (MC3-R), among others.

[0049] Orexin-A and orexin-B are neuropeptides found in the lateral hypothalamus. These neuropeptides and their associated receptors, OX1R and OX2R, have been demonstrated to stimulate the appetite of laboratory rats. Both increase food intake in a dose-related fashion, with orexin-A significantly more effective than orexin-B. Furthermore, when the food intake of the rats was limited, even more of the neuropeptides was produced, as might be expected of a hormone that physiologically regulates appetite.

[0050] Additional substances that may act on the hypothalamus to contribute to the development of eating disorders or the symptoms thereof include catecholamines, such as epinephrine and norepinephrine. Various adrenergic and noradrenergic cell groups in the medulla project to the paraventricular nucleus and the dorsomedial nucleus of the hypothalamus.

[0051] Additional substances that may act on the hypothalamus to retard or prevent development of eating disorders or the symptoms thereof include corticotropin releasing factor (CRF), bombesin, glucagon-like peptide 1, serotonin, and cholecystikinin.

For instance, the arcuate nucleus and the paraventricular nucleus receive serotonergic input from fibers in the raphe nuclei in the brainstem. Serotonin is believed to block the secretion of NPY. The ventromedial nucleus and the paraventricular nucleus of the hypothalamus also receive a cholecystokinin-containing projection relayed from the vagal nuclei via the parabrachial nucleus in the pons (i.e., the pontine taste center).

[0052] Low-frequency electrical stimulation (i.e., less than about 100-150 Hz) has been demonstrated to excite neural tissue, leading to increased neural activity. Similarly, excitatory neurotransmitters, agonists thereof, and agents that act to increase levels of an excitatory neurotransmitter(s) have been shown to excite neural tissue, leading to increased neural activity. Inhibitory neurotransmitters have been shown to inhibit neural tissue, leading to decreased neural activity; however, antagonists of inhibitory neurotransmitters and agents that act to decrease levels of an inhibitory neurotransmitter(s) tend to excite neural tissue, leading to increased neural activity.

[0053] High-frequency electrical stimulation (i.e., greater than about 100-150 Hz) is believed to have an inhibitory effect on neural tissue, leading to decreased neural activity. Similarly, inhibitory neurotransmitters, agonists thereof, and agents that act to increase levels of an inhibitory neurotransmitter(s) have an inhibitory effect on neural tissue, leading to decreased neural activity. Excitatory neurotransmitters have been demonstrated to excite neural tissue, leading to increased neural activity; however, antagonists of excitatory neurotransmitters and agents that act to decrease levels of an excitatory neurotransmitter(s) inhibit neural tissue, leading to decreased neural activity.

[0054] Electrical stimulation has been proposed for treating eating disorders. However, electrical stimulation was applied to the vagus nerve (United States Patent Numbers 5,188,104 and 5,263,480) or to the trigeminal and/or glossopharyngeal nerve (United States Patent Number 5,540,734). Deep Brain Stimulation (DBS) has also been proposed for the treatment of eating disorders. U.S. Patent Number 5,782,798 to Rise discloses a device for electrically stimulating and/or delivering a drug into the paraventricular nucleus, the ventromedial nucleus, or the lateral hypothalamus. These devices require significant surgical procedures for placement of electrodes, catheters, leads, and/or processing units. These devices may also require an external apparatus that needs to be strapped or otherwise affixed to the skin.

other circumstances and/or locations. Similarly, where an "inhibitory" drug is mentioned, this drug is acting in an inhibitory manner, although in other circumstances and/or locations, it may be an "excitatory" drug. In addition, stimulation of an area herein may include stimulation of cell bodies and axons in the area.

[0059] In some alternatives, an implantable signal generator and electrode(s) and/or an implantable pump and catheter(s) are used to deliver electrical stimulation and/or one or more stimulating drugs to specific areas in the brain. One or more electrodes are surgically implanted in the brain to provide electrical stimulation, and/or one or more catheters are implanted in the brain to infuse the stimulating drug(s).

[0060] In some embodiments, electrical stimulation is provided by one or more system control units (SCUs) that are small, implantable stimulators, referred to herein as microstimulators. The microstimulators of the present invention may be similar to or of the type referred to as BION® devices (see FIGS. 3A, 3B, and 3C). The following documents describe various details associated with the manufacture, operation and use of BION implantable microstimulators, and are all incorporated herein by reference:

Application/Patent/ Publication No.	Filing/Publication Date	Title
U.S. Patent 5,193,539	Issued Mar 16, 1993	Implantable Microstimulator
U.S. Patent 5,193,540	Issued Mar 16, 1993	Structure and Method of Manufacture of an Implantable Microstimulator
U.S. Patent 5,312,439	Issued May 17, 1994	Implantable Device Having an Electrolytic Storage Electrode
U.S. Patent 5,324,316	Issued June 28, 1994	Implantable Microstimulator
U.S. Patent 5,405,367	Issued April 11, 1995	Structure and Method of Manufacture of an Implantable Microstimulator
PCT Publication WO 98/37926	Published September 3, 1998	Battery-Powered Patient Implantable Device
PCT Publication WO 98/43700	Published October 8, 1998	System of Implantable Devices For Monitoring and/or Affecting Body Parameters
PCT Publication WO 98/43701	Published October 8, 1998	System of Implantable Devices For Monitoring and/or Affecting Body Parameters
U.S. Patent 6,051,017 (App. No. 09/077,662)	Issued April 18, 2000 (filed May 29, 1998)	Improved Implantable Microstimulator and Systems Employing Same
	Published September, 1997	Micromodular Implants to Provide Electrical Stimulation of Paralyzed Muscles and Limbs, by Cameron, et al., published in IEEE Transactions on Biomedical Engineering, Vol. 44, No. 9, pages 781-790.

[0061] As shown in FIGS. 3A, 3B, and 3C, microstimulator SCUs 160 may include a narrow, elongated capsule 152 containing electronic circuitry 154 connected to electrodes 172 and 172', which may pass through the walls of the capsule at either end. Alternatively, electrodes 172 and/or 172' may be built into the case and/or arranged on a catheter 180 (FIG. 3B) or at the end of a lead, as described below. As detailed in the referenced patents, electrodes 172 and 172' generally comprise a stimulating electrode (to be placed close to the target tissue) and an indifferent electrode (for completing the circuit). Other configurations of microstimulator SCU 160 are possible, as is evident from the above-referenced patent publications, and as described in more detail herein.

[0062] Certain configurations of implantable microstimulator SCU 160 are sufficiently small to permit placement in or adjacent to the structures to be stimulated. For instance, in these configurations, capsule 152 may have a diameter of about 4-5 mm, or only about 3 mm, or even less than about 3 mm. In these configurations, capsule length may be about 25-35 mm, or only about 20-25 mm, or even less than about 20 mm. The shape of the microstimulator may be determined by the structure of the desired target, the surrounding area, and the method of implantation. A thin, elongated cylinder with electrodes at the ends, as shown in FIGS. 3A, 3B, and 3C, is one possible configuration, but other shapes, such as cylinders, disks, spheres, and helical structures, are possible, as are additional electrodes, infusion outlets, leads, and/or catheters.

[0063] Microstimulator SCU 160, when certain configurations are used, may be implanted with a surgical insertion tool such as the tool specially designed for the purpose, or may be injected (e.g., via a hypodermic needle). Alternatively, microstimulator SCU 160 may be implanted via conventional surgical methods, or may be inserted using other endoscopic or laparoscopic techniques. A more complicated surgical procedure may be required for fixing the microstimulator in place.

[0064] The external surfaces of microstimulator SCU 160 may advantageously be composed of biocompatible materials. Capsule 152 may be made of, for instance, glass or ceramic to provide a hermetic package that will exclude water vapor but permit passage of electromagnetic fields used to transmit data and/or power. Electrodes 172 and 172' may be made of a noble or refractory metal, such as platinum, iridium,

tantalum, titanium, niobium or their alloys, in order to avoid corrosion or electrolysis which could damage the surrounding tissues and the device.

[0065] In certain embodiments of the instant invention, microstimulator SCU 160 comprises two, leadless electrodes. However, either or both electrodes 172 and 172' may alternatively be located at the ends of short, flexible leads as described in U.S. Patent Application No. 09/624,130, filed 7/24/2000, which is incorporated herein by reference in its entirety. The use of such leads permits, among other things, electrical stimulation to be directed more locally to targeted tissue(s) a short distance from the surgical fixation of the bulk of microstimulator SCU 160, while allowing most elements of the microstimulator to be located in a more surgically convenient site. This minimizes the distance traversed and the surgical planes crossed by the device and any lead(s). In most uses of this invention, the leads are no longer than about 150 mm.

[0066] As mentioned earlier, stimulation is provided in accordance with the teachings of the present invention by electrical stimulation and/or one or more stimulating drugs. The invention includes one or more system control units (SCUs). In the case of electrical stimulation only, SCUs include a microstimulator and/or an implantable pulse/signal generator (IPG), or the like. In the case of drug infusion only, an SCU comprises an implantable pump or the like. In cases requiring both electrical stimulation and drug infusion, more than one SCU may be used. Alternatively, when needed and/or desired, an SCU provides both electrical stimulation and one or more stimulating drugs.

[0067] As depicted in FIG. 4, some embodiments of SCU 160 may be (but are not necessarily) implanted beneath the scalp, such as in a surgically-created shallow depression or opening in the skull 140, for instance, in parietal bone 141, temporal bone 142, or frontal bone 143. In several embodiments, SCU 160 conforms to the profile of surrounding tissue(s) and/or bone(s), and is small and compact. This may minimize upward pressure applied to the skin or scalp, which pressure may result in skin erosion or infection. In various embodiments, SCU 160 has a diameter of about 75 mm, or only about 65 mm, or even less than about 55 mm. In these configurations, SCU thickness may be approximately 10-12 mm, or even less than about 10 mm.

[0068] As seen in the embodiments depicted in FIG. 5, one or more electrode leads 170 and/or catheters 180 attached to SCU 160 run subcutaneously, for instance, in a surgically-created shallow groove(s) in the skull, to an opening(s) in the skull, and pass through the opening(s) into or onto the brain parenchyma and surrounding tissue. Recessed placement of the SCU and the lead(s) and/or catheter(s) may decrease the likelihood of erosion of overlying skin, and may minimize any cosmetic impact.

[0069] In embodiments such as in FIG. 5, electrode(s) 172 are carried on lead 170 having a proximal end coupled to SCU 160. The lead contains wires electrically connecting electrodes 172 to SCU 160. SCU 160 contains electrical components 154 that produce electrical stimulation pulses that travel through the wires of lead 170 and are delivered to electrodes 172, and thus to the tissue surrounding electrodes 172. To protect the electrical components inside SCU 160, some or all of the case of the SCU may be hermetically sealed. For additional protection against, e.g., impact, the case may be made of metal (e.g. titanium) or ceramic, which materials are also, advantageously, biocompatible. In addition, SCU 160 may be configured to be Magnetic Resonance Imaging (MRI) compatible.

[0070] In some alternatives, the electrical stimulation may be provided as described in International Patent Application Serial Number PCT/US01/04417 (the '417 application), filed 02/12/2001, which application is incorporated herein by reference in its entirety. As such, the electrical stimulation of the present invention may be as provided in this PCT application, which is directed to a "Deep Brain Stimulation System for the Treatment of Parkinson's Disease or Other Disorders".

[0071] In the case of treatment alternatively or additionally constituting drug infusion, SCU 160 may contain at least one pump 162 for storing and dispensing one or more drugs through infusion outlet(s) 182 and/or catheter(s) 180 into a predetermined site(s) in the brain tissue. When a catheter is used, it includes at least one infusion outlet 182, usually positioned at least at a distal end, while a proximal end of the catheter is connected to SCU 160.

[0072] According to some embodiments of the invention, such as described in the previously referenced '417 application and as depicted in FIG. 5, at least one lead 170 is attached to SCU 160, via a suitable connector 168, if necessary. Each lead

includes at least two electrodes 172, and may include as many as sixteen or more electrodes 172. Additional leads 170' and/or catheter(s) 180' may be attached to SCU 160. Hence, FIG. 5 shows (in phantom lines) a second catheter 180', and a second lead 170', having electrodes 172' thereon, also attached to SCU 160. Similarly, the SCUs 160 of FIGS. 3A, 3B, and 3C have outlets 182, 182' for infusing a stimulating drug(s) and electrodes 172, 172' for applying electrical stimulation.

[0073] Lead(s) 170 of certain embodiments of the present invention may be less than about 5 mm in diameter, or even less than about 1.5 mm in diameter. Electrodes 172, 172' on leads 170, 170' may be arranged as an array, for instance, as two or more collinear electrodes, or even as four or more collinear electrodes, or they may not be collinear. A tip electrode may also be supplied at the distal end of one or more leads. In some embodiments, SCU 160 is programmable to produce either monopolar electrical stimulation, e.g., using the SCU case as an indifferent electrode, or bipolar electrical stimulation, e.g., using one of the electrodes of the electrode array as an indifferent electrode. Some embodiments of SCU 160 have at least four channels and drive up to sixteen electrodes or more.

[0074] SCU 160 (which herein refers to IPGs, implantable pumps, IPG/pump combinations, microstimulators for drug and/or electrical stimulation, other alternative devices described herein, and the like) contains, when necessary and/or desired, electronic circuitry 154 for receiving data and/or power from outside the body by inductive, radio frequency (RF), or other electromagnetic coupling. In some embodiments, electronic circuitry 154 includes an inductive coil for receiving and transmitting RF data and/or power, an integrated circuit (IC) chip for decoding and storing stimulation parameters and generating stimulation pulses (either intermittent or continuous), and additional discrete electronic components required to complete the electronic circuit functions, e.g. capacitor(s), resistor(s), coil(s), and the like.

[0075] SCU 160 also includes, when necessary and/or desired, a programmable memory 164 for storing a set(s) of data, stimulation, and control parameters. Among other things, memory 164 may allow electrical and/or drug stimulation to be adjusted to settings that are safe and efficacious with minimal discomfort for each individual. Specific parameters may provide therapy for various eating disorders and levels of

[0078] In embodiments such as shown in FIG. 5, SCU 160 includes a rechargeable battery as a power source/storage device 166. The battery is recharged, as required, from an external battery charging system (EBCS) 192, typically through an inductive link 194. In these embodiments, and as explained more fully in the earlier referenced '417 PCT application, SCU 160 includes a processor and other electronic circuitry 154 that allow it to generate stimulation pulses that are applied to a patient 208 through electrodes 172 and/or outlet(s) 182 in accordance with a program and stimulation parameters stored in programmable memory 164. Stimulation pulses of drugs include various types and/or rates of infusion, such as intermittent infusion, infusion at a constant rate, and bolus infusion.

[0079] According to certain embodiments of the invention, an SCU operates independently. According to various embodiments of the invention, an SCU operates in a coordinated manner with other SCU(s), other implanted device(s), or other device(s) external to the patient's body. For instance, an SCU may control or operate under the control of another implanted SCU(s), other implanted device(s), or other device(s) external to the patient's body. An SCU may communicate with other implanted SCUs, other implanted devices, and/or devices external to a patient's body via, e.g., an RF link, an ultrasonic link, or an optical link. Specifically, an SCU may communicate with an external remote control (e.g., patient and/or physician programmer) that is capable of sending commands and/or data to an SCU and that may also be capable of receiving commands and/or data from an SCU.

[0080] For example, some embodiments of SCU 160 of the present invention may be activated and deactivated, programmed and tested through a hand held programmer (HHP) 200 (which may also be referred to as a patient programmer and may be, but is not necessarily, hand held), a clinician programming system (CPS) 202 (which may also be hand held), and/or a manufacturing and diagnostic system (MDS) 204 (which may also be hand held). HHP 200 may be coupled to SCU 160 via an RF link 195. Similarly, MDS 204 may be coupled to SCU 160 via another RF link 196. In a like manner, CPS 202 may be coupled to HHP 200 via an infra-red link 197; and MDS 204 may be coupled to HHP 200 via another infra-red link 198. Other types of telecommunicative links, other than RF or infra-red may also be used for

this purpose. Through these links, CPS 202, for example, may be coupled through HHP 200 to SCU 160 for programming or diagnostic purposes. MDS 204 may also be coupled to SCU 160, either directly through the RF link 196, or indirectly through IR link 198, HHP 200, and RF link 195.

[0081] In certain embodiments, using for example, a BION microstimulator(s) as described in the above referenced patents, and as illustrated in FIG. 6, the patient 208 switches SCU 160 on and off by use of controller 210, which may be handheld. Controller 210 operates to control SCU 160 by any of various means, including sensing the proximity of a permanent magnet located in controller 210, sensing RF transmissions from controller 210, or the like.

[0082] External components for programming and providing power to various embodiments of SCU 160 are also illustrated in FIG. 6. When communication with such an SCU 160 is desired, patient 208 is positioned on or near external appliance 220, which appliance contains one or more inductive coils 222 or other means of communication (e.g., RF transmitter and receiver). External appliance 220 is connected to or is a part of external electronic circuitry appliance 230 which may receive power 232 from a conventional power source. External appliance 230 contains manual input means 238, e.g., a keypad, whereby the patient 208 or a caregiver 242 may request changes in electrical and/or drug stimulation parameters produced during the normal operation of SCU 160. In these embodiments, manual input means 238 includes various electro-mechanical switches and/or visual display devices that provide the patient and/or caregiver with information about the status and prior programming of SCU 160.

[0083] Alternatively or additionally, external electronic appliance 230 is provided with an electronic interface means 246 for interacting with other computing means 248, such as by a serial interface cable or infrared link to a personal computer or to a telephone modem or the like. Such interface means 246 may permit a clinician to monitor the status of the implant and prescribe new stimulation parameters from a remote location.

[0084] The external appliance(s) may be embedded in a cushion, pillow, or hat. Other possibilities exist, including a head band or other structure that may be affixed to the patient's body or clothing.

[0085] In order to help determine the strength and/or duration of electrical stimulation and/or the amount and/or type(s) of stimulating drug(s) required to produce the desired effect, in some embodiments, a patient's response to and/or need for treatment is sensed. For example, electrical activity of the brain (e.g., EEG), nerve activity (e.g., ENG), muscle activity (e.g., EMG), or other activity may be sensed. Additionally or alternatively, one or more neurotransmitter levels and/or their associated breakdown product levels, hormone levels, or other substances, such as ketone levels, cytokines, glucose, electrolytes, enzymes, medication, and/or other drug levels, levels of one or more catecholamines, and/or any other bloodborne substance may be sensed. For example, levels of one or more neurotransmitters, such as Neuropeptide Y (NPY) and/or serotonin, may be sensed. Levels of one or more hormones or other substances, such as adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), thyroid stimulating hormone (TSH), leptin, ghrelin, agouti-related protein (AGRP), orexin-A, orexin-B, cholecystokinin (CCK), glucagon, glucocorticoids, and the like may be sensed.

[0086] For example, when electrodes of SCU 160 are implanted adjacent to the arcuate nucleus 106 of the hypothalamus, a stimulating electrode of SCU 160, or other sensing means, may be used to sense changes in NPY level resulting from the electrical and/or drug stimulation applied to the arcuate nucleus 106. (As used herein, "adjacent" or "near" means as close as reasonably possible to targeted tissue, including touching or even being positioned within the tissue, but in general, may be as far as about 150 mm from the target tissue.)

[0087] Alternatively, an "SCU" dedicated to sensory processes communicates with an SCU that provides the stimulation pulses. The implant circuitry 154 may, if necessary, amplify and transmit these sensed signals, which may be digital or analog. Other methods of determining the required electrical and/or drug stimulation include measuring impedance, acidity/alkalinity (via a pH sensor), body mass, and other methods mentioned herein, and others that will be evident to those of skill in the art

upon review of the present disclosure. The sensed information may be used to control stimulation parameters in a closed-loop manner.

[0088] For instance, in several embodiments of the present invention, a first and second "SCU" are provided. The second "SCU" periodically (e.g. once per minute) records NPY level (or the level of some other substance, or an amount of electrical activity, etc.), which it transmits to the first SCU. The first SCU uses the sensed information to adjust electrical and/or drug stimulation parameters according to an algorithm programmed, e.g., by a physician. For example, the amplitude of electrical stimulation may be increased in response to increased NPY levels. In some alternatives, one SCU performs both the sensing and stimulating functions, as discussed in more detail presently.

[0089] While an SCU 160 may also incorporate means of sensing symptoms or other prognostic or diagnostic indicators of eating disorders, e.g., via levels of a neurotransmitter or hormone, it may alternatively or additionally be desirable to use a separate or specialized implantable device to record and telemeter physiological conditions/responses in order to adjust electrical stimulation and/or drug infusion parameters. This information may be transmitted to an external device, such as external appliance 220, or may be transmitted directly to implanted SCU(s) 160. However, in some cases, it may not be necessary or desired to include a sensing function or device, in which case stimulation parameters are determined and refined, for instance, by patient feedback, or the like.

[0090] Thus, it is seen that in accordance with the present invention, one or more external appliances may be provided to interact with SCU 160, and may be used to accomplish, potentially among other things, one or more of the following functions:

[0091] Function 1: If necessary, transmit electrical power from the external electronic appliance 230 via appliance 220 to SCU 160 in order to power the device and/or recharge the power source/storage device 166. External electronic appliance 230 may include an automatic algorithm that adjusts electrical and/or drug stimulation parameters automatically whenever the SCU(s) 160 is/are recharged.

- 0953036 " 4 03634
T000T 030E69
- [0099] 4. From the response data received at external appliance 230 from SCU 160, the stimulus threshold for obtaining a response is determined and is used by a clinician 242 acting directly 238 or by other computing means 248 to transmit the desired electrical and/or drug stimulation parameters to SCU 160 in accordance with Function 2.
- [0100] 5. When patient 208 desires to invoke electrical stimulation and/or drug infusion, patient 208 employs controller 210 to set SCU 160 in a state where it delivers a prescribed stimulation pattern from a predetermined range of allowable stimulation patterns.
- [0101] 6. To cease electrical and/or drug stimulation, patient 208 employs controller 210 to turn off SCU 160.
- [0102] 7. Periodically, the patient or caregiver recharges the power source/storage device 166 of SCU 160, if necessary, in accordance with Function 1 described above (i.e., transmit electrical power).

[0103] For the treatment of any of the various types and levels of severity of eating disorders, it may be desirable to modify or adjust the algorithmic functions performed by the implanted and/or external components, as well as the surgical approaches, in ways that would be obvious to skilled practitioners of these arts. For example, in some situations, it may be desirable to employ more than one SCU 160, each of which could be separately controlled by means of a digital address. Multiple channels and/or multiple patterns of electrical and/or drug stimulation might thereby be programmed by the clinician and controlled by the patient in order to deal with complex or multiple symptoms or dysfunctions.

[0104] In some embodiments discussed earlier, SCU 160, or a group of two or more SCUs, is controlled via closed-loop operation. A need for and/or response to stimulation is sensed via SCU 160, or by an additional SCU (which may or may not be dedicated to the sensing function), or by another implanted or external device. Sensed conditions may be one or more of body mass, impedance, acidity/alkalinity (via a pH sensor), electrical activity of the brain (e.g., EEG), nerve activity (e.g., ENG), muscle activity (e.g., EMG), or other activity. Additionally or alternatively, neurotransmitter

levels and/or their associated breakdown product levels, hormone levels, or other substances, such as ketone levels, cytokines, glucose, electrolytes, enzymes, medication, and/or other drug levels, levels of one or more catecholamines, and/or any other bloodborne substance may be sensed. For example, levels of one or more neurotransmitters, such as Neuropeptide Y (NPY) and/or serotonin, may be sensed. Levels of one or more hormones or other substances, such as adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), thyroid stimulating hormone (TSH), leptin, ghrelin, agouti-related protein (AGRP), orexin-A, orexin-B, cholecystokinin (CCK), glucagon, glucocorticoids, and the like may be sensed.

[0105] If necessary, the sensed information is transmitted to SCU 160. In some embodiments, the parameters used by SCU 160 are automatically adjusted based on the sensed information. Thus, the electrical and/or drug stimulation parameters are adjusted in a closed-loop manner to provide stimulation tailored to the need for and/or response to the electrical and/or drug stimulation.

[0106] For instance, as shown in the example of FIG. 7, a first SCU 160, implanted beneath the skin of the patient 208, provides a first medication or substance; a second SCU 160' provides a second medication or substance; and a third SCU 160" provides electrical stimulation via electrodes 172 and 172'. As mentioned earlier, the implanted devices may operate independently or may operate in a coordinated manner with other similar implanted devices, other implanted devices, or other devices external to the patient's body, as shown by the control lines 262, 263 and 264 in FIG. 7. That is, in accordance with certain embodiments of the invention, the external controller 250 controls the operation of each of the implanted devices 160, 160' and 160". According to various embodiments of the invention, an implanted device, e.g. SCU 160, may control or operate under the control of another implanted device(s), e.g. SCU 160' and/or SCU 160". That is, a device made in accordance with the invention may communicate with other implanted stimulators, other implanted devices, and/or devices external to a patient's body, e.g., via an RF link, an ultrasonic link, an optical link, or the like. Specifically, as illustrated in FIG. 7, SCU 160, 160', and/or 160", made in accordance with the invention, may communicate with an external remote control (e.g.,

patient and/or physician programmer 250) that is capable of sending commands and/or data to implanted devices and that may also be capable of receiving commands and/or data from implanted devices.

[0107] A drug infusion stimulator made in accordance with the invention may incorporate communication means for communicating with one or more external or site-specific drug delivery devices, and, further, may have the control flexibility to synchronize and control the duration of drug delivery. The associated drug delivery device typically provides a feedback signal that lets the control device know it has received and understood commands. The communication signal between the implanted stimulator and the drug delivery device may be encoded to prevent the accidental or inadvertent delivery of drugs by other signals.

[0108] An SCU made in accordance with the invention thus incorporates, in some embodiments, first sensing means 268 for sensing therapeutic effects, clinical variables, or other indicators of the state of the patient, such as body mass, impedance, pH, EEG, ENG, EMG, or the like. The stimulator additionally or alternatively incorporates second means 269 for sensing neurotransmitter levels and/or their associated breakdown product levels, medication levels and/or other drug levels, hormone, glucose, ketone, electrolytes, enzyme, and/or cytokine levels and/or changes in these or other substances in the blood plasma or local interstitial fluid. The stimulator additionally or alternatively incorporates third means 270 for sensing electrical current levels and/or waveforms supplied by another source of electrical energy. Sensed information may be used to control infusion and/or electrical parameters in a closed loop manner, as shown by control lines 266, 267, and 265. Thus, the sensing means may be incorporated into a device that also includes electrical and/or drug stimulation, or the sensing means (that may or may not have stimulating means) may communicate the sensed information to another device(s) with stimulating means.

[0109] According to some embodiments of the invention, the electrical and/or drug stimulation increases excitement of one or more of those areas of the brain that exhibit chronic decreased activity in patients with eating disorders relative to control subjects, thereby treating or preventing eating disorders and the symptoms and pathological consequences thereof. Such excitatory stimulation is likely to be produced

by low-frequency electrical stimulation (e.g., less than about 100-150 Hz), an excitatory neurotransmitter agonist(s) (e.g., acetylcholine), a medication that increases the level of an excitatory neurotransmitter (e.g., edrophonium), an excitatory hormone agonists(s), an inhibitory neurotransmitter antagonist(s) (e.g., bicuculline), an inhibitory hormone antagonist(s), corticotropin releasing factor (CRF) and/or its agonists, bombesin and/or its agonists, glucagon-like peptide 1 and/or its agonists, serotonin and/or its agonists, leptin and/or its agonists, ghrelin antagonists, AGRP antagonists, MC4-R agonists, MC3-R agonists, orexin-A antagonists, orexin-B antagonists, OX1R antagonists, OX2R antagonists, cholecystikinin and/or its agonists, and/or the like. For example, for patients suffering from obesity and/or the like, this excitatory stimulation may be applied to, among other places, one or more of the paraventricular nucleus 100, the ventromedial nucleus 104, and the nucleus of the solitary tract 110. As another example, for patients suffering from anorexia and/or the like, this excitatory stimulation may be applied to, among other places, one or both of the arcuate nucleus 106 and the lateral hypothalamic area 112.

[0110] According to other embodiments of the invention, the electrical and/or drug stimulation decreases excitement of one or more of those areas of the brain that exhibit chronic *increased* activity in patients with eating disorders relative to control subjects, thereby treating or preventing eating disorders. Such inhibitory stimulation is likely to be produced by high-frequency electrical stimulation (e.g., greater than about 100-150 Hz), an inhibitory neurotransmitter agonist(s) (e.g., GABA), a medication that increases the level of an inhibitory neurotransmitter, an inhibitory hormone agonist(s), an excitatory neurotransmitter antagonist(s) (e.g., atropine), an excitatory hormone antagonist(s), and/or the like. For example, for patients suffering from obesity and/or the like, this inhibitory stimulation may also/instead be applied to, among other places, one or both of the arcuate nucleus 106 and the lateral hypothalamic area 112. As another example, for patients suffering from anorexia or the like, this inhibitory stimulation may be applied to, among other places, one or more of the paraventricular nucleus 100, the ventromedial nucleus 104, and the nucleus of the solitary tract 110.

[0111] In most embodiments herein, excitatory stimulation may be produced by (but is not limited to) one or more of the following: low-frequency electrical stimulation

(e.g., less than about 100-150 Hz), an excitatory neurotransmitter agonist(s) (e.g., acetylcholine), a medication that increases the level of an excitatory neurotransmitter (e.g., edrophonium), an excitatory hormone agonists(s), an inhibitory neurotransmitter antagonist(s) (e.g., bicuculline), an inhibitory hormone antagonist(s), corticotropin releasing factor (CRF) and/or its agonists, bombesin and/or its agonists, glucagon-like peptide 1 and/or its agonists, serotonin and/or its agonists, leptin and/or its agonists, ghrelin antagonists, AGRP antagonists, MC4-R agonists, MC3-R agonists, orexin-A antagonists, orexin-B antagonists, OX1R antagonists, OX2R antagonists, cholecystokinin and/or its agonists, and/or the like. In most embodiments herein, inhibitory stimulation may be produced by (but is not limited to) one or more of the following: high-frequency electrical stimulation (e.g., greater than about 100-150 Hz), an inhibitory neurotransmitter agonist(s) (e.g., GABA, baclofen, muscimol), a medication that increases the level of an inhibitory neurotransmitter, an inhibitory hormone agonist(s), an excitatory neurotransmitter antagonist(s) (e.g., atropine), an excitatory hormone antagonist(s), and/or the like.

[0112] According to some embodiments of the invention, the stimulation inhibits the secretion of NPY by the NPY-secreting cells of the arcuate nucleus 106 of the hypothalamus for patients with obesity and/or the like. In addition to the inhibitory stimulation described earlier, insulin, leptin, CRF, serotonin, and/or the like may also/instead be used.

[0113] For patients with anorexia and/or the like, certain embodiments of the invention provide stimulation to activate the secretion of NPY by the NPY-secreting cells of the arcuate nucleus 106 of the hypothalamus. Such excitatory stimulation is likely to be produced as described earlier.

[0114] According to various embodiments of the invention, for patients with obesity and/or the like, the stimulation inhibits the effects of NPY on the paraventricular nucleus 100, the dorsomedial nucleus 102, the ventromedial nucleus 104, and/or any other neural tissue with receptors for NPY. Such inhibitory action is likely to be produced by high-frequency electrical stimulation, an antagonist(s) of NPY (e.g., PYX-1, BIBP 3226, 1229 U 91, and/or NGD 95-1), and/or the like applied to one or more of the

[illegible]

—

[0116] According to various embodiments of the invention, the stimulation inhibits the production of AGRP by the AGRP-producing cells of the arcuate nucleus 106 for patients with obesity and/or the like. In addition to the inhibitory stimulation described earlier, insulin and/or the like may also/instead be used.

[0117] For patients with anorexia and/or the like, some embodiments of the invention provide stimulation to activate and/or promote the production of AGRP by the AGRP-producing cells of the arcuate nucleus 106. Such excitatory stimulation is likely to be produced as described earlier.

[0118] According to certain embodiments of the invention, for patients with obesity and/or the like, the stimulation inhibits the effects of AGRP on the paraventricular nucleus 100, the dorsomedial nucleus 102, the arcuate nucleus 106, and/or any other neural tissue with receptors for AGRP. Inhibitory stimulation to these areas is likely to be produced as described earlier.

[0119] For patients with anorexia and/or the like, several embodiments of the invention provide stimulation to activate and/or promote the effects of AGRP on the paraventricular nucleus 100, the dorsomedial nucleus 102, the arcuate nucleus 106, and/or any other neural tissue with receptors for AGRP. Excitatory action in these areas may be produced by AGRP itself, an agonist(s) of AGRP, and/or as described earlier.

[0120] According to some embodiments of the invention, the stimulation acts as an agonist of MC4-R and/or MC3-R in the paraventricular nucleus 100, dorsomedial nucleus 102, and/or arcuate nucleus 106 for patients with obesity and/or the like. Such excitatory stimulation is likely to be produced as described earlier.

[0121] For patients with anorexia and/or the like, certain embodiments of the invention provide stimulation to act as an antagonist of MC4-R and/or MC3-R in the paraventricular nucleus 100, the dorsomedial nucleus 102, and/or the arcuate nucleus 106. Such inhibitory stimulation is likely to be produced as described earlier.

[0122] According to various embodiments of the invention, for patients with obesity and/or the like, the stimulation inhibits the production of orexins by the lateral hypothalamus 112, and/or inhibits the action of orexins, for instance by acting as an antagonist(s) of the orexin-A receptor (OX1R) and/or orexin-B receptor (OX2R), in the paraventricular nucleus 100 and/or ventromedial nucleus 104. Such inhibitory stimulation is likely to be produced as described earlier.

[0123] For patients with anorexia and/or the like, several embodiments of the invention provide stimulation to promote or enhance the production of orexins by the lateral hypothalamus, and/or promotes or enhances the action of orexins, for instance by acting as an agonist of OX1R and/or OX2R, in the paraventricular nucleus 100 and/or ventromedial nucleus 104. Such excitatory stimulation is likely to be produced as described earlier.

[0124] According to some embodiments of the invention, for patients with obesity and/or the like, the stimulation inhibits the effects of one or more catecholamines on the paraventricular nucleus 100, the dorsomedial nucleus 102, and/or any other neural tissue with receptors for catecholamines. Such inhibitory action is likely to be produced by high-frequency electrical stimulation, an antagonist(s) of the catecholamine(s) (e.g., prazosin, metoprolol, and/or carvedilol), and/or the like applied to at least one of the paraventricular nucleus 100 and the dorsomedial nucleus 102.

[0125] For patients with anorexia and/or the like, certain embodiments of the invention produce or enhance the effects of one or more catecholamines on the paraventricular nucleus 100, the dorsomedial nucleus 102, and/or other neural tissue with receptors for catecholamines. Such excitatory action is likely produced by low-frequency electrical stimulation, an agonist(s) of the catecholamine(s) (e.g., dextroamphetamine and/or sibutramine), one or more of the catecholamines themselves, and/or the like applied to at least one of the paraventricular nucleus 100 and the dorsomedial nucleus 102.

Alternatively, this orchestration may be programmed, and not based on a sensed condition.

[0133] Additional potential (but not necessary) uses of the present invention include, but are not limited to, treatment for and prevention of diabetes and other conditions caused or worsened by obesity and/or other eating disorders, via the promotion of normal metabolism and weight control.

[0134] While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the scope of the invention set forth in the claims.

0903006-10004